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EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nyuspatactions@ladas.com

Office Action Summary	Application No.	Applicant(s)	
	09/856,282	DAVIS, BONNIE M	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5,10-20,24-26 and 29-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,10-20,24-26 and 29-42* is/are rejected.

7)☒ Claim(s) *42* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/10/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 1/14/2010, are acknowledged and entered. Claims 1, 3-5, 10-20, 24-26, and 29-42 are pending and under examination.

Response to Arguments

Applicants' arguments, filed 1/14/2010, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

As correctly pointed out by Applicants, Faber as cited in the 35 U.S.C. 103 rejection of claims 39 and 40 is not available as prior art against these claims. Accordingly, new grounds of rejection not necessitated by amendment to the claims are set forth below and this Office Action is Non-Final.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 8/10/2009. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

Claim 42 is objected to because of the following informalities: in line 15 of claim 42, the phrase "...prior and during **to** desired sleep..." is not grammatically correct. It appears Applicant means to say, "...prior to and during desired sleep...". Appropriate correction is required.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-5, 10-20, 24-26, and 29-42 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In independent claims 1, 41, and 42, recitation of "...analogs of lycoramine and rivastigmine wherein said analogs of galanthamine or lycoramine are compounds...." renders the claims indefinite. It is not apparent whether analogs of rivastigmine are encompassed by the claimed compositions and methods or whether the claims are limited to only analogs of galanthamine or lycoramine.

Claims 1, 3-5, and 10-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 1, it is unclear whether "said compounds" as recited in lines 12-13 refers only to analogs of galanthamine or lycoramine or to any acetylcholinesterase inhibitor recited in the claims. The only recitation of "compound" in claim 1 is in the phrase, "...said analogs of galanthamine or lycoramine are compounds wherein...".

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-5, 10-19, 24-26, 29-37, 39, and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 88/08708** (Published Nov. 17, 1988), **Reimann *et al.*** (Psychiatry Research, 1994, vol. 51, pages 253-267), and **Conte *et al.*** (Biomaterials, 1993, vol. 14, no. 13, pages 1017-1023) in view of **Cummings *et al.*** (Alzheimer Dis. Assoc. Disord., 1997, vol. 11, Suppl. 4, pages S1-S9) and **Ross *et al.*** (JAGS, Jan. 1998, vol. 46, pages 119-120).

Claimed Invention

The instant claims recite dosage forms comprising a centrally-acting acetylcholinesterase inhibitor (*e.g.*, galanthamine) formulated so as to delay the activity of the acetylcholinesterase inhibitor for a predetermined period of from four to twelve hours and methods of treating Alzheimer's disease comprising administration of such dosage forms.

Teachings of WO 88/08708

WO 88/08708 teaches compounds of formula (I) for use in the treatment of Alzheimer's disease (Abstract). Such compounds are galanthamine-analogues as recited in claims 1, 3-5, 10-19, 29-37, and 41-42 (pages 9-17).

Regarding claims 10-19 and 29-36, WO '708 teaches that R_1 and R2, which correspond to the methoxy group and hydroxy group in galanthamine, respectively, can be hydrogen, hydroxyl, or alkoxy of 1-6 carbons or alkyl or aryl carbamates (pages 10-14).

The compounds of the invention are taught to be inhibitors of acetylcholinesterase (page 38).

Compositions for administration to patients having Alzheimer's disease, including sustained release delivery formulations, are taught at page 24, first and second paragraph.

With respect to the claimed half life of from one to eleven hours as recited in the instant claims, the half life of any compound is a property of that compound and thus not separable from the compound itself. Therefore, because WO 88/08708 teaches the claimed compounds, the properties of these compounds that Applicants recite in the instant claims are necessarily present.

WO 88/08708 thus teaches, suggests, and motivates compositions comprising galanthamine and galanthamine analogs for the treatment of Alzheimer's disease. WO 88/08708 does not teach a formulation wherein acetylcholinesterase inhibition is avoided for a predetermined period of from four to twelve hours as recited in the instant claims.

Teachings of Riemann et al.

Riemann *et al*. teaches that some investigators have stressed the similarity of the effects of cholinomimetics on healthy sleep to baseline sleep patterns of depressed patients (page 254, second paragraph) and that galanthamine is a cholinesterase inhibitor used to treat Alzheimer's disease (page 254, third paragraph). In addition, Riemann *et al*. disclose that galanthamine increases the time awake and the number of awakenings in healthy patient compared to patients not receiving galanthamine (Table 3; paragraph bridging pages 260 and 261). Here, the skilled artisan is provided with the necessary motivation to develop controlled release formulations of galanthamine in order to avoid waking a patient from sleep.

Regarding claim 39, Reimann *et al*. teaches that because of peripheral side effects of 15 mg galanthamine, subjects were administered a peripheral muscarinic blocker (N-methylscopolaminehydrobromide). Such peripheral side effects include hypersalivation, hyperhydrosis, nausea, disturbed sleep, nightmares, and feelings of restlessness (Table 1).

Teachings of Conte et al.

Conte *et al*. teach methods of formulating pharmaceutical active agents in press-coated tablets for time-programmed release of drugs (Abstract). The delay in release start is taught to not be influenced by the core composition and depends only on the shell formulation (*id*.).

Suitable drugs for such time-programmed release include active agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity (*e.g*., psychotropic active drugs) (page 1017, left column, second full paragraph).

The press-coated tablets taught in Conte *et al*. release drugs at a specific rate, but the release starts only after a well defined period of time (page 1017, right column, first full paragraph).

With respect to the delay periods recited in claims 1, 3-4, and 24-25 (*i.e.*, 4 to 12 hours, 6 to 9 hours, or 8 to 12 hours), Conte *et al.* teach such delay periods, *e.g.*, 240 minutes, 480 minutes, and 720 minutes (Figures 6, 7, and 8).

Teachings of Cummings et al.

Cummings *et al.* is provided as evidence that cholinergic agents as recited in the instant claims were considered by those skilled in the art to be "psychotropic agents", and thus reasonably encompassed by the teachings of Conte *et al.*, who disclose "psychotropic active drugs" as suitable drugs for time-programmed release. In this regard, Cummings *et al.* state that, "[C]holinergic compounds are unique **psychotropic agents** that exhibit disease specificity, exerting beneficial effects only in diseases such as AD with cholinergic deficits" (Abstract).

Teachings of Ross et al.

Ross *et al.* teach that the cholinesterase inhibitor, donepezil, when administered to Alzheimer's patients at the recommended nighttime administration, leads to insomnia and nightmares (page 119, right column). When the nighttime acetylcholinesterase inhibitor administration was stopped, the insomnia and nightmares also stopped. The authors suggested changing from nighttime to morning administration. When the acetylcholinesterase inhibitor was administered in the morning, no further sleep problems were noted. The authors suggest that by administering donepezil in the morning, subsequent insomnia might be significantly reduced or eliminated.

Secondary Considerations

Applicant explains that it was known in the art that the pattern of brain acetylcholine is elevated release just before and during the time of activity, and reduced release during sleep (citing Kametani, 1991 and Mizuno, 1991 at page 5 of instant specification).

Applicant further explains that it was known in the art that the brain content of acetylcholine exhibits a reciprocal relationship with release patterns, presumably representing stored neurotransmitter. (citing Saito, 1974 at page 5 of instant specification) and that acetylcholinesterase activity, which keeps synaptic acetylcholine concentrations low, peaks

during the subjective night, and is lowest during activity periods (citing Schiebeler, 1974 at page 5 of instant specification).

As explained by Applicant, humans are sensitive to the systemic administration of the acetylcholinesterase inhibitors physostigmine and galanthamine late in the day or at night, when endogenous cholinergic activity is low and "these disturb sleep and produce awakenings" (citing Sitaram, 1979 and Reimann, 1994 at page 6 of the instant specification).

Applicant provides no working examples and no evidence of unexpected results have been proffered.

Findings of Fact

1. Applicant's claim 1 recites a dosage form of a pharmaceutical composition which comprises an effective amount of a centrally-acting acetylcholinesterase inhibitor for the treatment of Alzheimer's disease selected from the group consisting of galanthamine, lycoramine, analogs of galanthamine, analogs'of lycoramine and rivastigmine; said compounds having a half-life of from one to eleven hours wherein the acetylcholinesterase inhibitor is formulated so as to delay its activity for a predetermined period of from four to twelve hours such that acetylcholinesterase inhibition is avoided during such predetermined period. (Claims filed 1/14/2010)
2. Applicants' claim 41 recites a method of treatment of an Alzheimer's patient comprising administering a delayed release dosage form of a pharmaceutical composition which comprises an effective amount of a centrally-acting acetylcholinesterase inhibitor for the treatment of Alzheimer's disease selected from the group consisting of galanthamine, lycoramine, analogs of galanthamine, analogs'of lycoramine and rivastigmine, wherein the dosage form is formulated such that the half life of the activity of the acetylcholinesterase inhibitor and the degree of delayed release are

selected such that the formulation may be administered to the patient such that release of acetylcholinesterase inhibitor is avoided for the next anticipated sleep time and wherein administration of the drug is at an appropriate time to achieve such results. (Claims filed 1/14/2010)

3. Applicant's specification explains that the pattern of brain acetylcholine is elevated release just before and during the time of activity, and reduced release during sleep. (Page 5 of instant specification, citing Kametani, 1991 and Mizuno, 1991)
4. Applicant's specification explains that the brain content of acetylcholine exhibits a reciprocal relationship with release patterns, presumably representing stored neurotransmitter. (Page 5 of instant specification, citing Saito, 1974)
5. Applicant's specification explains that acetylcholinesterase activity, which keeps synaptic acetylcholine concentrations low, peaks during the subjective night, and is lowest during activity periods. (Page 5 of instant specification, citing Schiebeler, 1974)
6. Applicant's specification explains that humans are sensitive to the systemic administration of the acetylcholinesterase inhibitors physostigmine and galanthamine late in the day or at night, when endogenous cholinergic activity is low and "these disturb sleep and produce awakenings". (Page 6 of the instant specification, citing Sitaram, 1979 and Reimann, 1994)
7. Applicant's claims 1, 41, and 42 identify galanthamine, lycoramine, analogs of galanthamine, analogs of lycoramine and rivastigmine as centrally-acting acetylcholinesterase inhibitors for the treatment of Alzheimer's disease (Claims filed 1/14/2010)
8. WO 88/08708 teaches galanthamine-analogues for the treatment of Alzheimer's disease. (Abstract; pages 9-17)

9. WO 88/08708 teaches that galanthamine-analogues of the invention are inhibitors of acetylcholinesterase. (Page 38)
10. WO 88/08708 teaches compositions comprising galanthamine-analogues for administration to patients having Alzheimer's disease, including sustained release delivery formulations. (Page 24, first and second paragraph)
11. Reimann et al. teach that the cholinesterase inhibitor galanthamine increases the time awake and the number of awakenings in healthy patient compared to patients not receiving galanthamine. (Table 3; paragraph bridging pages 260 and 261)
12. Conte *et al.* teaches methods of formulating pharmaceutical active agents in press-coated tablets for time-programmed release of drugs (Abstract).
13. Conte *et al.* teaches that suitable drugs for time-programmed release include active agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity (*e.g.*, psychotropic active drugs) (page 1017, left column, second full paragraph).
14. Cummings *et al.* teach that cholinergic compounds are unique psychotropic agents that exhibit disease specificity, exerting beneficial effects only in diseases such as AD with cholinergic deficits. (Abstract)
15. Ross *et al.* teach that the cholinesterase inhibitor, donepezil, when administered to Alzheimer's patients at the recommended nighttime administration, leads to insomnia and nightmares (page 119, right column)
16. Ross *et al.* teach that when nighttime acetylcholinesterase inhibitor administration is stopped, insomnia and nightmares also stop.

Examiner's Determination of Obviousness

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate a acetylcholinesterase inhibitor such galanthamine or galanthamine-analogues as instantly claimed into compositions providing delayed release of the active agent for use in the treatment of Alzheimer's disease.

The skilled artisan would have been motivated to do so because Conte *et al.* teach that psychotropic active drugs are agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity and thus suitable for incorporation into the press-coated delayed release tablets. Cummings *et al.* provides factual evidence that one skilled in the art at the time the invention was made would recognize cholinergic agents such as the claimed cholinesterase inhibitors as psychotropic agents.

WO 88/08708 teaches that galanthamine was known in the art as an agent useful in treating Alzheimer's disease "and related dementias" (page 1) and inhibits acetylcholinesterase (page 38). While WO 88/08708 does not teach delayed release formulations, one skilled in the art would recognize that the acetylcholinesterase inhibitors disclosed therein are psychotropic agents as taught in Conte *et al.* and Cummings *et al.*

Ross *et al.* and Reimann *et al.* provide further motivation to formulate acetylcholinesterase inhibitors in delayed release dosage forms. In this regard, Ross *et al.* teach that administration of the acetylcholinesterase inhibitor donepezil at night produces results in insomnia and nightmares. The authors therefore suggest administration in the morning rather than at night. Reimann *et al.* teach that the cholinesterase inhibitor galanthamine increases the time awake and the number of awakenings in healthy patient compared to patients not receiving galanthamine. The skilled artisan would thus have found it obvious that morning administration of an acetylcholinesterase inhibitor could be readily obtained by providing a dosage form that could be administered at night (*e.g.*, before bedtime), but wherein the release of active agent is delayed until morning. Such delayed-release dosage forms are disclosed in Conte *et al.* Conte *et al.* provides methods of formulating compositions that will aid in patient compliance, *i.e.*, a patient can take a pill at night before bed and not have to "remember" to take the pill in the

morning after they awake because drug release will have been delayed while they are sleeping and will commence release just prior to or after they wake up.

In view of the combined teachings of the cited prior art, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate acetylcholinesterase inhibitors in delayed-release dosage forms for the treatment of Alzheimer's disease. The claimed acetylcholinesterase inhibitors were known in the art and the prior art provides the means and motivation to formulate psychotropic agents in delayed release dosage forms. Further, in view of the teachings of Ross *et al.* and Applicant's admission that humans are sensitive to the systemic administration of the acetylcholinesterase inhibitors physostigmine and galanthamine late in the day or at night, when endogenous cholinergic activity is low and "these disturb sleep and produce awakenings" (page 6 of the instant specification, citing Sitaram, 1979 and Reimann, 1994), the skilled artisan would recognize that by delaying the release of an acetylcholinesterase inhibitor until morning, disturbances of sleep, awakenings, and nightmares due to acetylcholinesterase inhibition could be avoided.

Response to Arguments

Applicant's arguments have been carefully considered but they are not deemed to be persuasive. While Applicant's arguments are directed to the previous rejection of claims 1, 3-5, and 10-19 over WO 88/08708, Conte *et al.*, and US 5,585,375, the Examiner will address Applicant's arguments as they pertain to the new ground of rejection set forth *supra*.

Firstly, Applicant argues that WO 88/087708 teaches away from the present invention because it teaches that one should aim at a constant level of active compound in the patient's blood stream. Applicant argues that the Examiner cannot modify the teachings of a reference if the proposed modification would change the "principle of operation of prior art invention being modified" (citing MPEP 2143.01(VI)). This is not persuasive because modifying the release of an acetylcholinesterase inhibitor would not, as alleged by Applicant, "change the principle operation" of the prior art. Acetylcholinesterase would still be inhibited and Alzheimer's disease would still be treated if the acetylcholinesterase inhibitor release were delayed until a patient awakes. As admitted by Applicant, humans are sensitive to the systemic administration of the acetylcholinesterase inhibitors physostigmine and galanthamine late in the day or at night, when

endogenous cholinergic activity is low and "these disturb sleep and produce awakenings" (citing Sitaram, 1979 and Reimann, 1994 at page 6 of the instant specification).

Secondly, Applicant argues that "even now" conventional wisdom is to keep blood levels of acetylcholinesterase inhibitors constant. Applicant argues that the most commonly used drug for the treatment of Alzheimer's disease continues to be administered in formulations that are active during sleep and at the time of the present invention, the general consensus was that one should not vary the dosage level of Alzheimer's drugs between the day and night. This argument is not persuasive because the fact that acetylcholinesterase inhibitors had not been previously administered in a dosage form to delay their release in the prior art does not negate the obviousness of doing so. In fact, the entire basis of 35 U.S.C. 103 is that while the claimed invention is novel (*i.e.*, has not been previously done) it would nonetheless have been obvious to one of ordinary skill in the art at the time the invention was made. In the instant case, there is clear motivation for one skilled in the art to formulate compositions of acetylcholinesterase inhibitors for treating Alzheimer's disease wherein said acetylcholinesterase inhibitors are formulated so as to delay their activity. As admitted by Applicant, administration of acetylcholinesterase inhibitors late in the day or at night disturb sleep and produce awakenings (citing Sitaram, 1979 and Reimann, 1994 at page 6 of the instant specification). Applicant further admits that it was known to those skilled in the art that the pattern of brain acetylcholine is elevated release just before and during the time of activity, and reduced release during sleep.

Thirdly, Applicant argues that Conte states that suitable drugs for time-programmed release include active agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes in circadium rhythmicity. Applicant argues that the acetylcholinesterase inhibitor galanthamine is not known to have daily variations in pharmacokinetics and that Alzheimer's disease does not occur at certain times of the day and not others. However, while Alzheimer's disease itself does not occur at certain times of the day and not others, acetylcholine levels and acetylcholinesterase levels do have variations in their levels based on the time of day. It is well established in the art and is admitted by Applicant that in Alzheimer's disease, the primary and universal neurochemical abnormality is a deficit of acetylcholine. This is precisely why inhibitors of acetylcholinesterase are used to treat Alzheimer's disease, i.e., to inhibit breakdown of acetylcholine. When acetylcholine levels are

highest (i.e., before and during the time of activity), there is clearly more need to inhibit acetylcholinesterase activity so as to maintain high levels of acetylcholine. When acetylcholine levels are lowest (i.e., during times of sleep), there is clearly less need to inhibit acetylcholinesterase because high acetylcholine levels during sleep are not necessary or desired.

Fourthly, Applicant argues that the Examiner's conclusion that that a patient being treated for Alzheimer's would not be in need of acetylcholinesterase inhibitor medication while they are sleeping is an unreferenced supposition because prior art cited by Applicant discloses that REM sleep was long known to be cholinergic and that the cholinergic deficit in Alzheimer's disease was believed to underlie REM reductions in Alzheimer's patients. However, Applicant admits in the instant specification that the art also teaches that administration of acetylcholinesterase inhibitors late in the day or at night disturb sleep and produce awakenings (citing Sitaram, 1979 and Reimann, 1994 at page 6 of the instant specification). Further, the newly cited Ross et al. reference teaches that the acetylcholinesterase inhibitor donepezil, when administered at night, produces insomnia and nightmares. Thus, one skilled in the art would recognize that delaying release of an acetylcholinesterase inhibitor until after a period of sleep would not disturb sleep or produce awakening of the Alzheimer's patient.

Lastly, Applicant argues that the question of whether drugs for treatment of Alzheimer's disease fall within Conte's definition of psychotropic drugs has been considered before and that Conte does not indicate whether or not cholinesterase inhibitors were considered to be psychotropic drugs. In response, the Examiner respectfully directs Applicant to Cummings et al. (Alzheimer Dis. Assoc. Disord., 1997, 11 Suppl. 4, pages S1-S9), which was cited by Applicants in the IDS filed 9/22/2008. Cummings et al. disclose, unequivocally, that "[C]holinergic compounds are unique **psychotropic drugs** that exhibit disease specificity, exerting beneficial effects only in diseases such as AD with cholinergic deficits" (Abstract). Cholinesterase inhibitors are clearly psychotropic drugs whose effects depend on physiological and/or physiopathological changes of circadian rhythmicity as disclosed in Conte et al. because they inhibit an enzyme whose expression is not constant throughout the day (acetylcholinesterase activity peaks during the subjective night, and is lowest during activity periods).

Claims 20 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 88/08708** (Published Nov. 17, 1988), **Reimann *et al.*** (Psychiatry Research, 1994, vol. 51, pages 253-267), and **Conte *et al.*** (Biomaterials, 1993, vol. 14, no. 13, pages 1017-1023) in view of **Cummings *et al.*** (Alzheimer Dis. Assoc. Disord., 1997, vol. 11, Suppl. 4, pages S1-S9) and **Ross *et al.*** (JAGS, Jan. 1998, vol. 46, pages 119-120) as applied to claims 1, 3-5, 10-19, 24-26, 29-37, 39, and 41-42 above, and further in view of **Nordberg *et al.*** (Drug Safety, 1998, vol. 19, no. 6, pages 465-480).

WO 88/08708, Reimann *et al.*, Conte *et al.*, Cummings *et al.*, and Ross *et al.* teach as discussed *supra*. The references do not teach the acetylcholinesterase inhibitor, rivastigmine, as specifically recited in claims 20 and 38.

However, Nordberg *et al.* compare the tolerability and pharmacology of cholinesterase inhibitors in the treatment of Alzheimer's disease. In this regard, the reference teaches that cholinesterase inhibitors are currently the most established treatment strategy in Alzheimer's disease and that three cholinesterase inhibitors are in clinical use: tacrine, donepezil, and rivastigmine (Abstract). Further, Nordberg *et al.* teach that other cholinesterase inhibitors such as galanthamine (also recited in the instant claims) are under clinical evaluation (*id.*).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to formulate rivastigmine as instantly claimed into compositions providing delayed release of the active agent for use in the treatment of Alzheimer's disease. The skilled artisan would have been motivated to do so because Conte *et al.* teach that psychotropic active drugs are agents having significant daily variations in pharmacokinetics and/or drug effects depending on physiological and/or physiopathological changes of circadian rhythmicity and thus suitable for incorporation into the press-coated tablets taught therein.

In this regard, it is noted that Nordberg *et al.* teach that rivastigmine inhibits acetylcholinesterase and was known in the art as an agent useful in treating Alzheimer's disease (Abstract; pages 475-476), a reasonable interpretation of which is that rivastigmine is a psychotropic drug as evidenced by Cummings et al.

Further, one of ordinary skill in the art would recognize that a patient being treated for Alzheimer's dementia or behavioral abnormalities would not be in need of medication while they are sleeping because acetylcholine levels would be lower than when the patient is awake. As

such, Conte *et al.* provides methods of formulating compositions that will also aid in patient compliance, *i.e.*, a patient can take a pill at night before bed and not have to "remember" to take the pill in the morning after they awake because drug release will have been delayed while they are sleeping and will commence release just prior to or after they wake up.

Further still, as discussed *supra*, it was known in the art that cholinesterase inhibitors disturb sleep, produce awakenings, and induce nightmares. As such, the skilled artisan would recognize the benefit of administering a dosage formulation of an acetylcholinesterase inhibitor at night, wherein the release of the acetylcholinesterase inhibitor is delayed until the patient awakes.

Claim 40 is rejected under 35 U.S.C. 103(a) as being unpatentable over **WO 88/08708** (Published Nov. 17, 1988), **Reimann *et al.*** (Psychiatry Research, 1994, vol. 51, pages 253-267), and **Conte *et al.*** (Biomaterials, 1993, vol. 14, no. 13, pages 1017-1023) in view of **Cummings *et al.*** (Alzheimer Dis. Assoc. Disord., 1997, vol. 11, Suppl. 4, pages S1-S9) and **Ross *et al.*** (JAGS, Jan. 1998, vol. 46, pages 119-120) as applied to claims 1, 3-5, 10-19, 24-26, 29-37, 39, and 41-42 above, and further in view of **Kennedy *et al.*** (J. Clin. Invest., 1984, vol. 74, pages 972-975) (newly cited).

WO 88/08708, Reimann *et al.*, Conte *et al.*, Cummings *et al.*, and Ross *et al.* teach as discussed *supra*. While Reimann *et al.* teach co-administration of the muscarinic blocker N-methylscopolaminehydrobromide to reduce the peripheral side effects of galanthamine, the references do not teach the administering of propantheline bromide or glycopyrrolate to reduce the peripheral effects of the claimed acetylcholinesterase inhibitors.

However, Kennedy *et al.* teach administration of propantheline before infusion of the centrally active cholinesterase inhibitor physostigmine in order to "prevent the peripheral effects of physostigmine" (page 972, right column). The authors state the "we blocked peripheral muscarinic effects [of physostigmine] with either methscopolamine or propantheline" (page 973, paragraph bridging left and right columns)

Accordingly, in the absence of a showing of unexpected results commensurate in scope with the claims, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer acetylcholinesterase inhibitors as recited in the instant

claims in conjunction with a compound that reduces its peripheral effects, such as propantheline as motivated and suggested by Kennedy *et al.* or methylscopolaminehydrobromide as suggested and motivated by Reimann *et al.* Kennedy *et al.* teach that propantheline and methylscopolamine are both effective in blocking the peripheral muscarinic effects of centrally-acting acetylcholinesterase inhibitors.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/James D Anderson/
Primary Examiner, Art Unit 1614

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